So, we're going to finish now by just talking more about this amazing immune system we have, the adaptive immune system.

As I said on Friday, this is really an astonishing recognition system that just plays a key role in us being able to survive in this world that's full of bacteria, and yeast, and fungi, and viruses, parasites. There are things just all the time trying to do us in, and the reason we don't succumb is because we have this amazing immune system. And there are several features about it which I summarized the other day.

One is its diversity. It has this incredible ability to recognize entities, including things that are synthesized in a lab that had never been seen on Earth before.

It's amazing in terms of that side of it. Coupled with this is this incredible specificity. As I indicated the other day, for example, if it was seeing a benzene ring with a methyl on it, it might be able to recognize this, but it could tell the difference from having the methyl over here. It's got that level of sophistication. In spite of that, in spite of the fact that it can recognize everything else, it's able to avoid self recognition, which is a bit of a trick if you think about it, that you have a system that's able to see essentially anything, including things that never existed before. And how does it avoid seeing all of our molecules, and all the many, many things that makes us up? So, it has to be able to tell self from non-self.

And then, I also talked about this memory aspects of the immune system, that if you get exposed to a virus or bacterium or something, but the first immune response is relatively weak.

But then if you get subsequently exposed, you get a very powerful response. And that's the principle of a vaccine. If you think someone is going to be exposed to chickenpox but they haven't had it, if you could somehow elicit the initial response without making them sick by using a killed virus or something like that; polio is one of the examples you hear about in the paper right at the moment. Then, if someone does encounter that virus or that bacterium, because that's second response, it's very quick and it's very powerful, and that's what vaccines are all about. So, the issue, I guess, today is how does that happen? And this is one of these amazing insights into biology that's come by an application of all these tools, recombinant DNA, and sequencing, and all the fancy sort of things we've been talking about in the past few lectures.

So, the first part I need to let you know, is there are two parts to this immune response, or two kinds of responses.

One's called the humoral response and one's called the cellular response. And this takes place in the plasma of your blood. So, in the liquid part of the blood if you spin down the red cells and the white cells, what you're left with is the plasma.

And, what this humoral response response does, it's able to target bacteria, viruses, proteins.

And the recognition is done by a special kind of protein called antibodies. And I'll tell you about that in just a moment because they're a very important class of protein in this Earth. And the cellular immune response is carried out by a special kind of white blood cell.

For this lecture I think I'll just abbreviate those as WBC if I need it. What this targets is not the actual pathogen itself. But it targets cells that are infected with a virus or a bacterium, etc. and that might seem to be even a little bit more of a trick. It's hard enough probably to figure out how to take something that's an entity like a virus that's floating around your blood and figure out how to find something that binds to it.

What do you do if the thing's gone into one of your own cells and it's hiding out in their replicating in the same way that, let's say, a phage does or something like that How do you see one of your own cells that's been infected by something like that? And there is a special type of cells called cytotoxic T cell that's very important. It's often abbreviated as that.

So let me first say a word about antibodies. These are proteins that consist of four polypeptide chains. Two of the chains are bigger. So they're called heavy chains. There's two of those. And there are two chains that are smaller, so those are usually called light chains. So, there's four of them altogether.

And, ignoring secondary structure and stuff for the moment, let me just sort of give you an idea of how these are laid out.

These are the two heavy chains.

And these are joined together by disulfide bridges.

You remember disulfide bridges? If you had two cystines they can form a covalent bond between them under oxidizing conditions.

So, those heavy chains are locked together. They're actually physically covalently joined. In fact, there's the light chains here. So, this is the light. And this part up here is highly variable between different antibodies.

And the part down here is constant between antibodies.

And it's this huge amount of variability that the body produces many, many, many types of antibodies, and then figures out which ones will work to find the particular entity it's trying to recognize.

And I'll come back and tell you in a moment how that is done.

There is a diagram of what I showed you, but of course these are proteins. They have three-dimensional structures, and so if you were to look at them with the secondary structure showing, you can see the different, especially here, a lot of beta sheets should be leaping out at you.

Now, the part where the recognition is done is up at this end.

So, it's essentially right here. And here's a little movie. You could see how the thing looks in three dimensional space.

You see the part that's over on the left at the moment; that's the light chain and the blue chain is that part of the heavy chain complex with the light chain. And here is the, it's been tilted up this way so this is the yellow and blue part you were looking at And the recognition pocket is right at the end of that. And at this picture, it's showing how a particular protein was shown in red.

This is an anti-body that can very, very precisely recognize that particular protein. You can't really tell it from the three-dimensional shape shown on the left because it just shows the secondary structure. But, if you could see the full space filling model, you'd be amazed. The surfaces are absolutely complementary. It goes back to one of those principles I've said over and over and over again that so much of biology works by having complementary surfaces.

And there's a little movie you could see how this thing is setting up there at the top. So, these antibodies are produced by a special type of what are called B cells.

These are cells that play roles in the humoral part of the immune system. And they're called plasma cells. And each plasma cell makes one particular antibody. And that's it.

So you have many different types of plasma cells, but each one only expresses one particular gene that encodes one particular antibody.

So, for years, this is something that people struggled with just conceptually. They could sort of calculate that there were so many antibodies that if your entire genome was nothing but antibody genes, we still wouldn't have enough DNA to account for all this ability to recognize things. So, some other principle had to be involved. And there are all sorts of speculations about what it was.

I had shown you, I'd managed to not get Bob Horvitz's thing on here, but this then, who is our fourth Nobel laureate, I've been sort of working through these.

Susumu Tonegawa, who is in the cancer center, he's in the biology department. He's also heading, now, this

Picower Center of learning and memory. So, since doing this work I'm telling you about on the immune system, he's gone to do some wonderful stuff more on the big problem of how we learn, and trying to get more molecular insights into that process.

But what Susumu managed to figure out was that this variation and diversity in the immune system was, at its roots, a combinatorial sort of process. So, if you look in the DNA of a zygote, so that's the fertilized egg. We're just getting started with one of our cells. You've got a single cell. We're looking in the DNA to see what would happen. We come to the part of the DNA that's involved in producing antibodies. What he found was that if you looked along the DNA, there were sequences that looked like part of the stuff that you'd find in antibodies, but there were a whole series of them. So, he called this particular segment V1, V2, V3, up to VN. There were a whole set of these basically side by side by side by side.

There are about 300 of these in humans. And then down the DNA a little bit he found another set of sequences that are all variations of each other. And these were given D1, D2, D3, D4, up to DN.

And there are many of these. And then down the DNA a little farther, there were three other sections that were called joining segments. They were called J1, J2, J3. And a little bit farther down there was a block of DNA coding the constant part of this polypeptide chain that goes into an antibody.

And what Susumu Tonegawa was able to show, and this led to the Nobel Prize. So, what happens during the development of these B cells is there are rearrangements. And a lot of DNA is thrown around.

And the basic strategy is to take, if you think this as being column A, you take one from column A, one from column B, just picking them randomly, one from column C over here, and throw away everything else.

So you might have, for example, in one B cell, you might have V32, D15, J2, and then the constant region.

And, what's in between is an intron that will be spliced out at the time that the gene's expressed. In another B cell, you might have V11, D22, J3. So, this rearrangement is random in the sense of which V segment is chosen, which D segment is chosen, and which J segment. I don't mean that it all just joins together in a completely uncontrolled way. And then the rest of the DNA is deleted.

So a consequence of this, is each B cell expresses only one antibody. It's true that they're diploid, but only one chromosome is expressed. So that's how they avoid, you can imagine they might make to two. But they only make one.

In the process, as you can see, that part is random. Furthermore, the joining events are what I think you could call sloppy.

And this leads to even more variation than you would have imagined simply looking at the number of segments.

So, what this part of the process does is it explains why the system can be has the diversity it has, because it's using this combinatorial process. If you know the number you can calculate how many possible combinations there are.

But then there's much more variation because when it joins together a little segments that are joined are done in a sloppy way so that the DNA sequence that shows up where the joints occur doesn't look like anything that was in the DNA at all. It was something like a polymerase that wasn't very faithful copying and making mistakes as it went along. So what the system does, is it doesn't get you a response. It just explains why there is so much diversity, and why it is that I can go into the lab and synthesize a compound that's never been on this earth before, inject a rabbit to it, and the rabbit will probably produce an antibody that's able to recognize that. That's because it's made this whole set of them. And they all are going to have somewhat different surfaces. And they make so many that one of those surfaces is going to fit the molecule that I'm testing.

You can sort of see, that's only part of the trick.

So, how do you now get an immune response? Because you've got millions of these things. But what you now need is a whole lot of one particular antibody that's going to recognize the pathogen that you are being exposed to. And the principle of that is really cute. It's a process called clonal selection.

And the idea is that each B cell displays a sample of its antibody on its surface. So, we might think of it this sort of way, that after this process is through we have one B cell. Of course, these are way out of proportion. The cells would be huge, and these would be molecules.

So, they're small. But here would be an antibody that can recognize squares, say, this one would have an antibody that could recognize triangle. This one would have an antibody that could recognize a semicircle and so on, millions and millions of different shapes. And these cells don't divide, though. They've been made, and they just sit there.

And then, when you stimulate them with an antigen, and I used that word the other day, an antigen is just anything that will elicit an immune response. It could be a piece of a foreign protein, carbohydrate, just about anything that's a small molecule you've made in the lab. But let's say we exposed now this individual to an antigen, which in this case can fit into that receptor. And what happens, then, this one becomes stimulated to divide. So what we have now is this B cell that has this antigen stuck into its binding pocket on the sample of its antibody. And then, the cells divide and they give rise to two populations. They give rise to the plasma cells, which are very short-lived, on the order of a few days.

And what these do, so they would look like this, what they do is secrete antibodies into the plasma.

So what you end up with, then, are a lot of these antibodies that have exactly the specificity that the original sample had on the outside of that particular B cell. This takes a few days. So back when we were talking about the discovery of DNA, I was telling you about Streptococcus pneumonia, and you get infected by the Streptococcus.

And there would be this period of five or six days where this person was very sick, and then either they'd survive or they didn't survive. If they survived, they'd been able to mount an immune response and make these antibodies before they got killed by the bacteria. And the reason it takes a few days is when you start out there could be just one B cell that's able with an antibody, makes an antibody that is capable of recognizing the capsule.

Maybe there are a few. Anyway, but they were very, very tiny number, and there were probably a lot of bacteria.

So what had to happen, then, is that the original cell or small number of cells that could recognize the Streptococcus had to be amplified. They had to make a lot of plasma cells that have the potential to make the antibody, and then they had to secrete the antibody into the plasma. And I'll tell you in just a minute some of the strategies that that uses to help kill the pathogen.

And the other population, just before I go on there, are what are called memory cells. There's not as many of these made, but they're very long-lived. And so, what they have is exactly the same capacity to make the same antibody, but they're not actively dividing.

They'll just sit there, float around in your bloodstream, and then if you get a second exposure to the antigen, you get a very fast and strong response because the selection for finding the cells that had antibodies that can recognize the antigen has already been done.

And there's already a few of them around, and then after you do that then you're able to make, once again, the binding of the antigen stimulates these guys to start dividing.

They make a lot of plasma cells. And going back to the principal of vaccination, your first response is fairly modest.

But if you get a second response, what you're doing now is the memory cells are already there. They have the specificity for recognizing the antigen in question. And you can make a whole lot of them. So, if you had chickenpox when you were little, you have memory cells that know how to recognize the chickenpox virus.

And then when your kid gets chickenpox like mine did, I didn't get sick because I had memory cells that were able to recognize that. OK, so what happens if you get an antibody? How does this help the organism, or in our case

someone like you or me, avoid getting sick?

So there are a couple of strategies. One we might think of is bind and block. For example, you are a virus and you get covered by antibodies. Viruses: it's exactly the same logic as bacteriophage, except that instead of affecting a bacterial cell a virus would be infecting one of our cells.

And as the virus has receptors or something, it has to recognize something on my cell, in order to attach and then to inject its DNA. So if we've got an antibody sitting here, then it can't find its way to the host cell.

And then, there are a couple of other ways. They can target for destruction. And there's basically two ways. There's something called the complement system, that if it is able to recognize, say, the bacterial cell and their antibodies are sticking to the outside, what the complement system does is it's able to make little pores in the membrane of the pathogen.

And I think one of the things I hope you will remember is that one of the secrets of life is that we have to keep that membrane around there.

We have to keep all of our insides in, and the rest of the world outside. We have hydrogen ion gradients across the membrane.

So, if you want to kill a cell and you, say, insert a protein that has a little hole and it, and that thing sits and sticks in the membrane, that cell is dead. It can't maintain an ion gradient, and things can leak out through the hole.

So that's one of the ways of killing it. The other ways are macrophages.

These are a type of white blood cell, as well, are very good at recognizing bacteria that have antibodies stuck to the outside. And in fact, that was the principle of that. We have the Streptococcus, and we have the capsule.

And you may remember that little movie I showed of a white blood cell that was trying to eat it, and it couldn't get hold of the thing, whereas we saw another example where a bacterium without a capsule, there was sort of principle I said is that the white blood cell was able to recognize the bacterium and then it pinches it off inside of a membrane bubble. And I sort of said at least in principle that there is another little bubble with poisons, and it brings it together so that you have the bacterium and the poison together inside of some intracellular compartment, so that macrophages know how to kill a bacterium if they bring it inside.

The problem in the case of something like Streptococcus was being able to recognize it because it couldn't get hold of that capsule.

So, those antibodies that guy made during that five day thing decorate the outside of the capsule because their

specificity is to recognize the capsule and bind to it. But a macrophage, even if it couldn't get hold of the bacterium with a capsule is able to ingest something that has antibodies stuck on the outside.

And once it gets inside, it can kill the bacterium.

In fact, immunologists call this process opsinization, which is derived from the Greek words for seasoning, like putting salt on your food. And the idea was that when they were giving that word, with these macrophages, which liked to eat bacteria, they have a little seasoning that they have these little antibodies decorating their outsides.

So here you can see it least in the humoral response how you generate a whole lot of diversity. Then this principle of what's called clonal selection identifies a B cell that's able to make an antibody that can recognize the particular pathogen or molecule that you're being exposed to amplify that, make a lot of antibodies, and then it can either just stick to the pathogen like a virus and mess it up that way, or it can decorate it if it's something like a bacterium, and then pull in a couple of other systems that are capable of killing the pathogen. I mean, it's an absolutely amazing system.

It sounded like science fiction when I first heard about it.

When I heard people talking about it, everyone could see there was an information theory problem. How do you encode all that information with just this amount of DNA in a cell?

Now we understand. And there's even another part that I'm leaving out here. But once this whole thing has been selected, there's another whole round of sort of refinement where the cells do kind of a very kind of localized mutagenesis one base pair at a time in the vicinity of this binding pocket.

And they're able to make, if they're given more time and more exposure to the antigen, they can make a better and better binding surface until you begin to approach sort of the theoretical maximum. Now, the T cell, in this case this involves the cytotoxic T cells, and they have a specific recognition molecule on their surface. It's called the T cell receptor.

And in this case, it's attached.

So, this is the membrane of the T cell. And this is the cytoplasm down on this side. There's a little bit of the protein that goes into that. And then there's an alpha helix that goes through, and then a segment that comes up like this. And there's another chain that does the same thing.

So, there are two segments that span the membrane.

This thing is anchored in the membrane.

And then it's essentially the same principle as with antibodies.

There's a variable region, and there's a constant region.

And to a first approximation anyway the logic by which the cell generates a huge, diverse set of T cell receptors is the same logic that underlies the generation of a whole lot of different antibodies by taking segments, joining them, picking them randomly out of column A, column B, and then joining them together, sloppy joining all the other processes to increase the pool of diversity. Now, what these B cells are able to do, then, these T cells are able to do is something quite remarkable.

We have on our cells, this is, say, one of my cells, little sort of proteins that function as sort of display cases or something. And what they do is they show samples of all of the different proteins that are inside us at any given moment. Proteins are turned over, and chopped up, and things are recycled and so on.

So there are always little peptides, little pieces of proteins around.

And, the display case, if you will, has got a major histocompatibility complex, which is usually abbreviated as MHC because it's such an unwieldy name. And there are many, many alleles of MHC in the population, which means that we each have, for the most part, a sort of individually designed display case for showing these peptides. The property of these display cases, they take some little piece of a protein just a few amino acids long, it binds into the display case, and that sticks on the outside of our cell. And so we have a lot of these. And so on the surface of our cells are these little individualized MHC display cases showing little samples of the peptides of the proteins from the proteins that are inside us.

So, if everything is fine, all of the peptides that are in the display cases are our own. And I'll tell you in a minute why that doesn't cause a problem. But then if you get infected by a virus, and it injects DNA or its RNA inside of you and then starts to replicate, now you have some virus proteins that don't belong to you.

They get chopped into pieces, and they begin to appear on these major histocompatibility display cases. So if you think here, this could be, perhaps, a little piece of, let's call it self protein, it could be a little piece of my own DNA polymerase or something like that. And over in this one, let's say we have a little piece of a viral protein.

So that's something that would not be normally there.

So what this T-cell receptor does is it recognizes, so this is non-self or foreign. What the T-cell receptor does is it recognizes these foreign peptides. But it does it in the context of the display case. Otherwise the peptides would

be floating around. So, in essence, the T-cell receptor, if this is a cytotoxic T cell it's able to see the individual display case with a bit of viral protein in it.

And then it knows that it should kill that cell because it's got something in it that shouldn't be there. I mean, it's a brutal but very effective strategy. If we applied it here, I go around if I found any of you had a cold, I could just take a gun and shoot you and it would cut down on the number of sick days for the rest of us because it wouldn't spread the infection.

But in essence, at a molecular level, that's the strategy. Try to identify a cell that's got something inside it that shouldn't be there, and then the cytotoxic T cells kill that. And let me just show you a couple of quick movies of this.

At this point, these will be the last protein structures you're going to see from me, I think. Here's a representation of that T cell just as a cartoon as you see it in a textbook.

Here it is. This is the binding pocket up here.

And there's a little tiny peptide, nine and amino acids from the HIV virus bound in here. Somebody did a crystal structure, and was able to work that out. And, if you look at it in three dimensions, you'll see how beautifully this little binding pocket and the peptide lies in there.

So that red part is the piece of chalk, and the other part is what I'm describing as my hand. It's not a bad analogy, actually, even on a structural level. And then, here's another representation.

This is sort of showing the hand with a piece of peptide in it.

And then the T cell is able to see this whole thing in recognize it.

And, if you look at it in a structural form, here's the little peptide. This is the part, the display case you're looking at. And here's the T cell receptor now fitting down in seeing the peptide in the context of this major histocompatibility antigen. And again, these things are all beautifully complementary a three dimensional level.

Again, at the heart of this is the principle of complementary surfaces fitting together that underlies so much biology. What's this?

This is a tumor cell. These are cytotoxic T cells that have recognized this tumor cell is doing something it shouldn't that a normal cell wouldn't do. And it's attacking it, and it's killing them. So, not only does the cellular immune response help us against things like infections from virus and bacteria, it also will help prevent cancer. So obviously there must be some trick here to why we don't see our own peptides. This is the self versus non-self

And it's a relatively simple principle.

So, distinguishing self versus non-self is a problem throughout this whole part of the immune system.

And here's the principle. During embryogenesis, the cell makes, the organism I guess, makes the assumption. I mean obviously it's not thinking about it.

This is a way of understanding what's happening.

It makes the assumption that no pathogens are present.

Any B or T cell recognizing something must be recognizing itself.

And so, it deletes those B and T cells. This process is given a name.

It's called education. And it happens in this organ called thymus. So, and then after birth, then it switches. And now B and T cells, if they recognize something, the body makes the assumption it must be a pathogen. And it goes after it.

We have this huge human disease where that goes awry: rheumatoid arthritis, or multiple sclerosis are cases where the self versus non-self recognition has broken down. OK, so for example multiple sclerosis, a very difficult disease, because there's a gradual deterioration of the nervous system.

And what happens is the body of the person with that mounts an immune response against the sheath that covers the nerves, and then that sheath gets destroyed, and that the nervous system, somebody with multiple sclerosis, starts to break down. And so, if you lose this self versus non-self you get what's called an autoimmune disease. You may have heard that phrase. It's very important.

It's a very tough thing if you have one of these. But that's what lies at the heart of it. And people still don't know, but there is certainly some evidence for some of these that are triggered by a bacterial infection. So, it could be that perhaps maybe a bacterial protein looked close enough to one of your own proteins, that somehow you got antibodies against the bacterium, and then it turned out it could also recognize something in your body.

There are some other immune diseases you probably heard of, the baby in a bubble kind of thing. There are a few people who were born who have no immune response at all because one of the basic pieces for doing those DNA gymnastics I talked about isn't there.

Those people have no B cells or T cells. They die unless they are absolutely shielded from everything else. And that's one of those cases when gene therapy, if you could get that gene into that person, they'd have an immune

system and they could live.

There are other kinds of immune deficiencies that are less extreme, but nevertheless, people will be susceptible to infection.

The other one which I've already talked about, but now you can see in another context is AIDS, Acquired Immune Deficiency Syndrome.

And I told you what the HIV virus does is it injects its RNA.

That makes a DNA copy. It goes into protein. The cells that it affects our special type of T cell called T helper cells.

What they are doesn't matter so much, but what's important to know is they're needed for both branches of the immune system.

They play roles in the humoral response and cellular response.

So, someone who gets infected with HIV, what happens is the virus is replicating in these helper T cells. And so their immune system is slowly, slowly being knocked away. And the last thing, which I won't have time to talk about, but if you have an allergy, that's an overreaction of the immune system. So this is my last lecture.

I've got to let you guys go. It's been a true pleasure to talk to you; A real honor to meet many of you. And many of you put a lot of effort into those little answers. I really, really appreciate that.

For those who'd rather not be here, I hope that somewhere down the line when you're confronted with a medical situation dealing with your parents, your child, yourself, whatever it is, that some of the stuff that you heard will reemerge to help you with those decisions. And I wish you the best of luck for the rest of the course, and the rest of your careers at MIT and beyond. Thanks very much. And as I leave, too, I've had the pleasure of just having an incredible teaching staff.

I don't think you guys know how hard they work behind the scenes, but thanks to all of you for being with me.